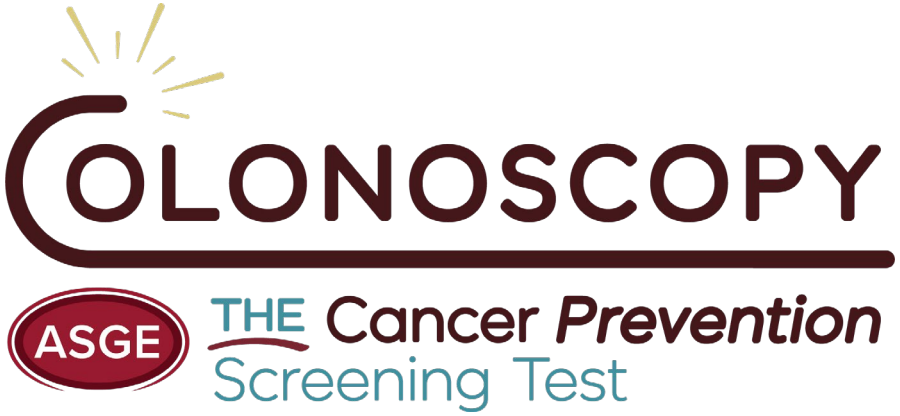
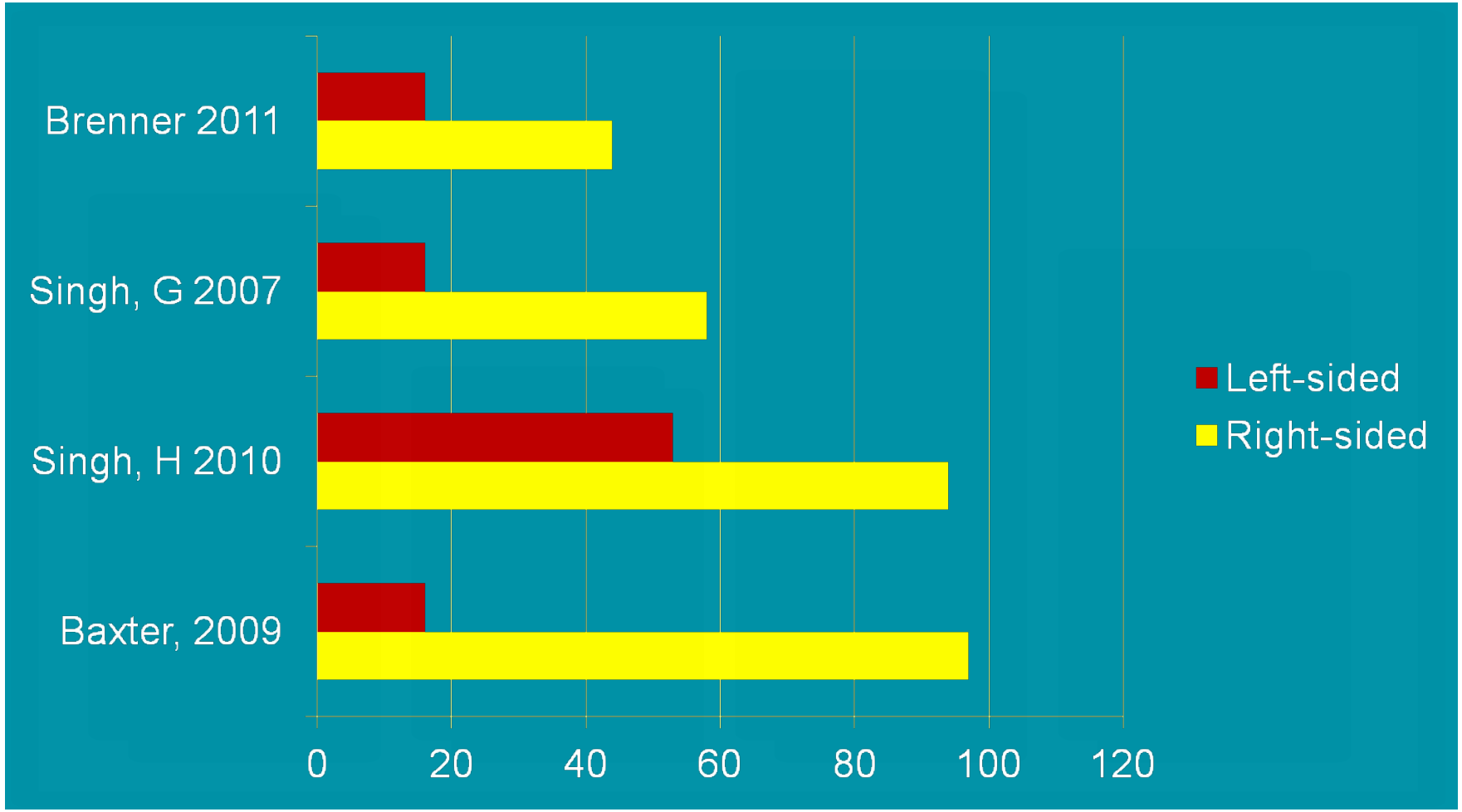
Colorectal Cancer Screening and Surveillance



Residual Risk after Colonoscopy: Right vs Left Colon



Colorectal Cancer Molecular Basis

Pathway	Frequency	Genes	MSI	Precursor	Speed
CIN	70-75%	*APC* *k-ras* *p53*	No	Adenoma	Slow
Lynch	3%	*MLH1* *MSH2* *MLH6* *PMS2*	Yes	Adenoma	Fast
CIMP	20-30%	*BRAF*	Sometimes	Serrated	Can be fast

Two Classes of Precancerous Lesions in the Colorectum

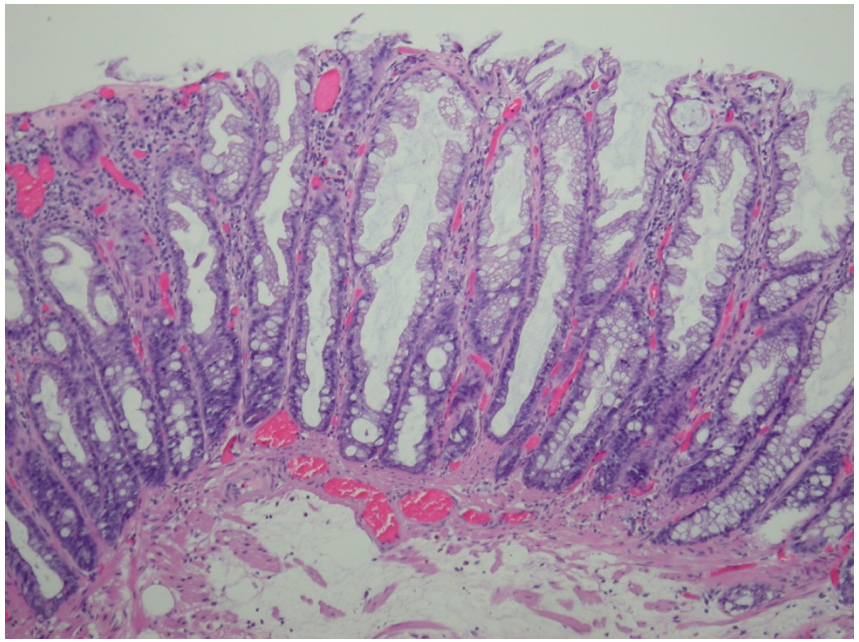
- Conventional adenomas
  - Dysplasia grade (low vs high)
  - Villousity (tubular vs tubulovillous vs villous)
- Serrated class
  - Sessile serrated polyp/adenoma
  - Traditional serrated adenoma

Expanded Terminology of Serrated Lesions (WHO)

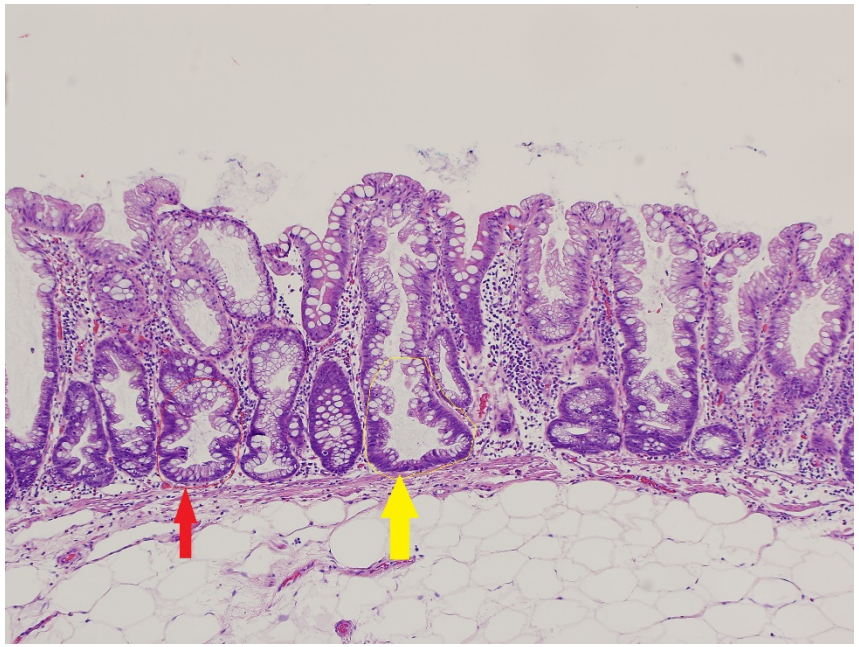
- Hyperplastic polyp (HP)
  - Goblet cell HP
  - Microvesicular HP
  - Mucin Poor HP
- Sessile serrated adenoma/polyp (SSA/P)
  - With cytological dysplasia
  - Without cytological dysplasia
- Traditional serrated adenoma (TSA)

Pathologic Differentiation of SSA/P from HP

MVHP



SSA/P

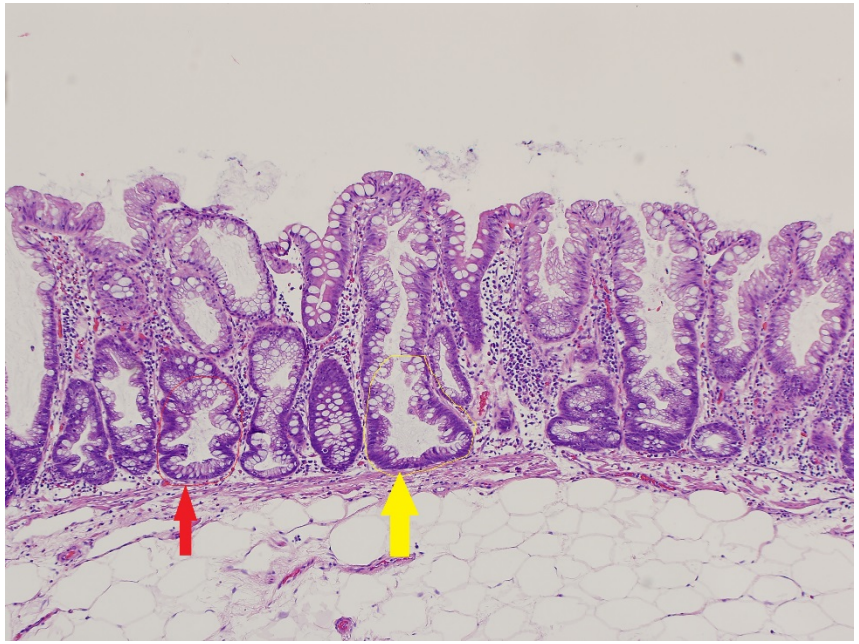


Agreement for Pathologic Interpretation of SSA/P vs HP

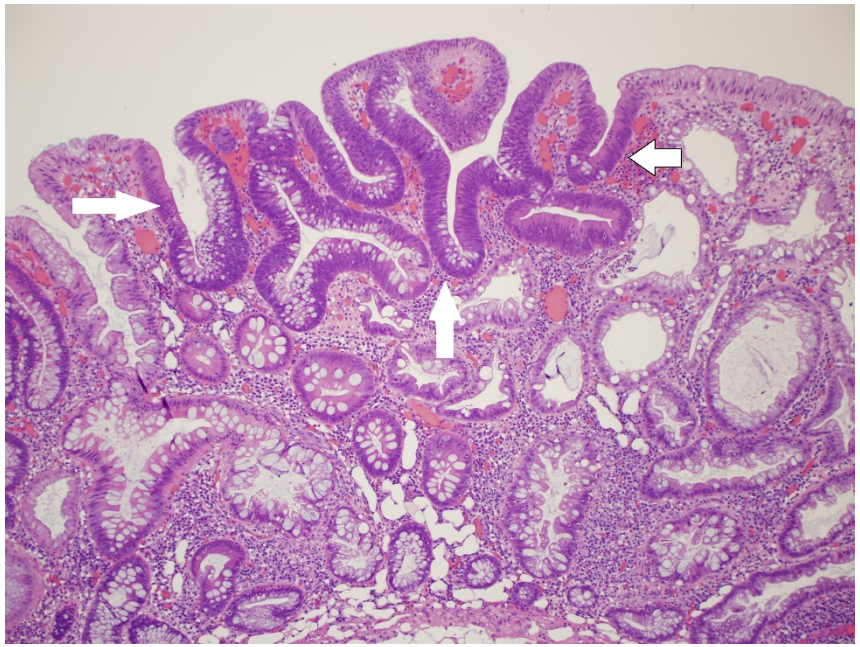
- Glatz et al Am J Clin Pathol 2007
  - SSA commonly read as HP
  - TSA commonly read as TVA
- Khalid et al World J Gastroenterol 2009
  - 30-80% of proximal HPs in 2001 read as SSP by experts; kappas 0.14-0.38

SSA/P Without and With Cytological Dysplasia

SSA/P without dysplasia



SSA/P with dysplasia



The Serrated Pathway

Hyperplastic polyp

? ↓ ?

Sessile serrated adenoma/polyp

↓ probably slow

SSA/P with cytologic dysplasia

↓ sometimes fast

CIMP colon cancer

2416 SSA/Ps

	mean age
• SSA/P	61y
• SSA/P with LGD	66y
• SSA/P with HGD	72y
• SSA/P with cancer	76y

- Lash J Clin Pathol 2010;63:681-6

Histology of Colon Polyps – Reliable or Not?

Yes

- Serrated vs conventional adenoma
- Cancer or no cancer

Not very

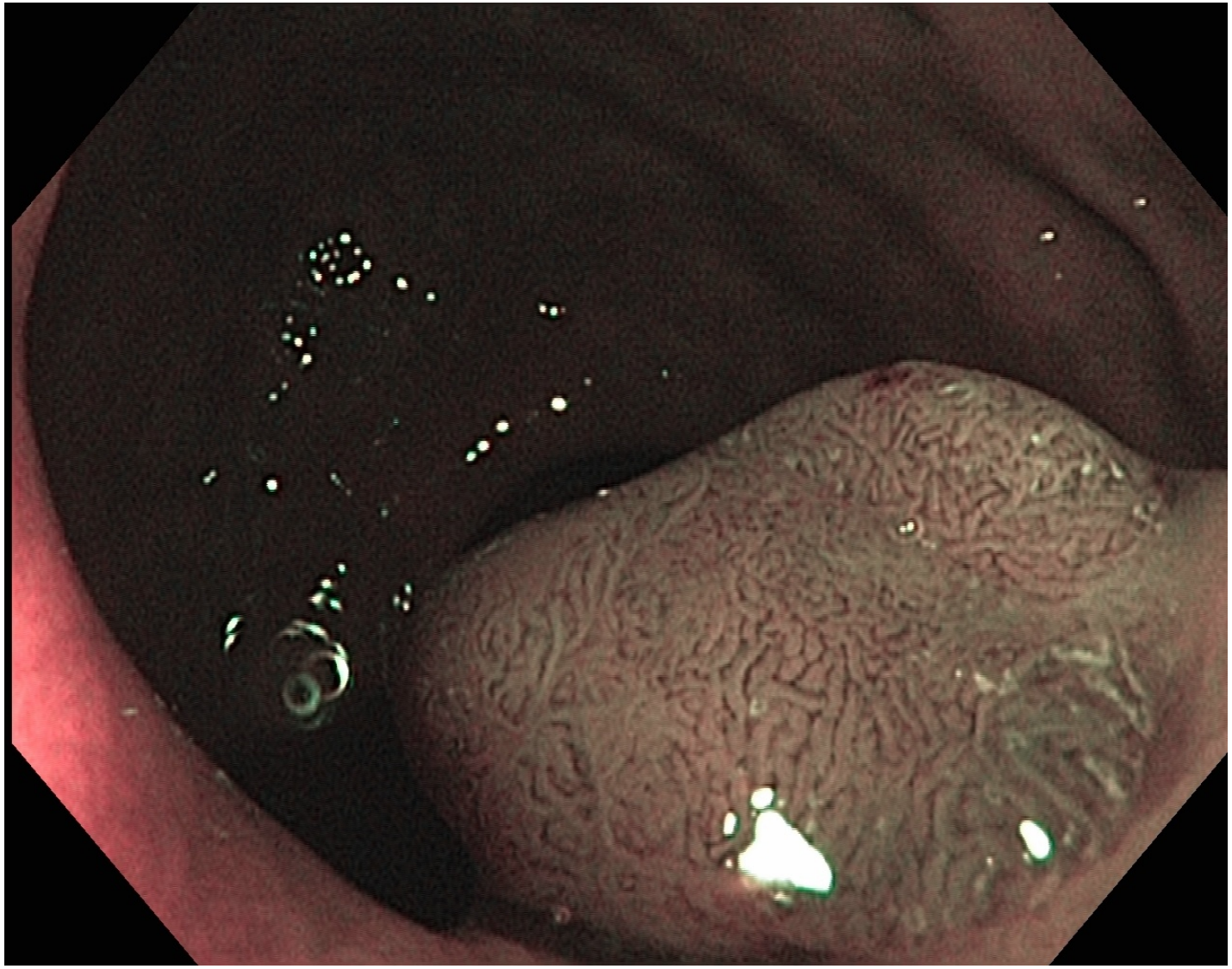
- Tubular vs tubulovillous
- HGD vs LGD
- Tumor differentiation
- SSA/P vs HP

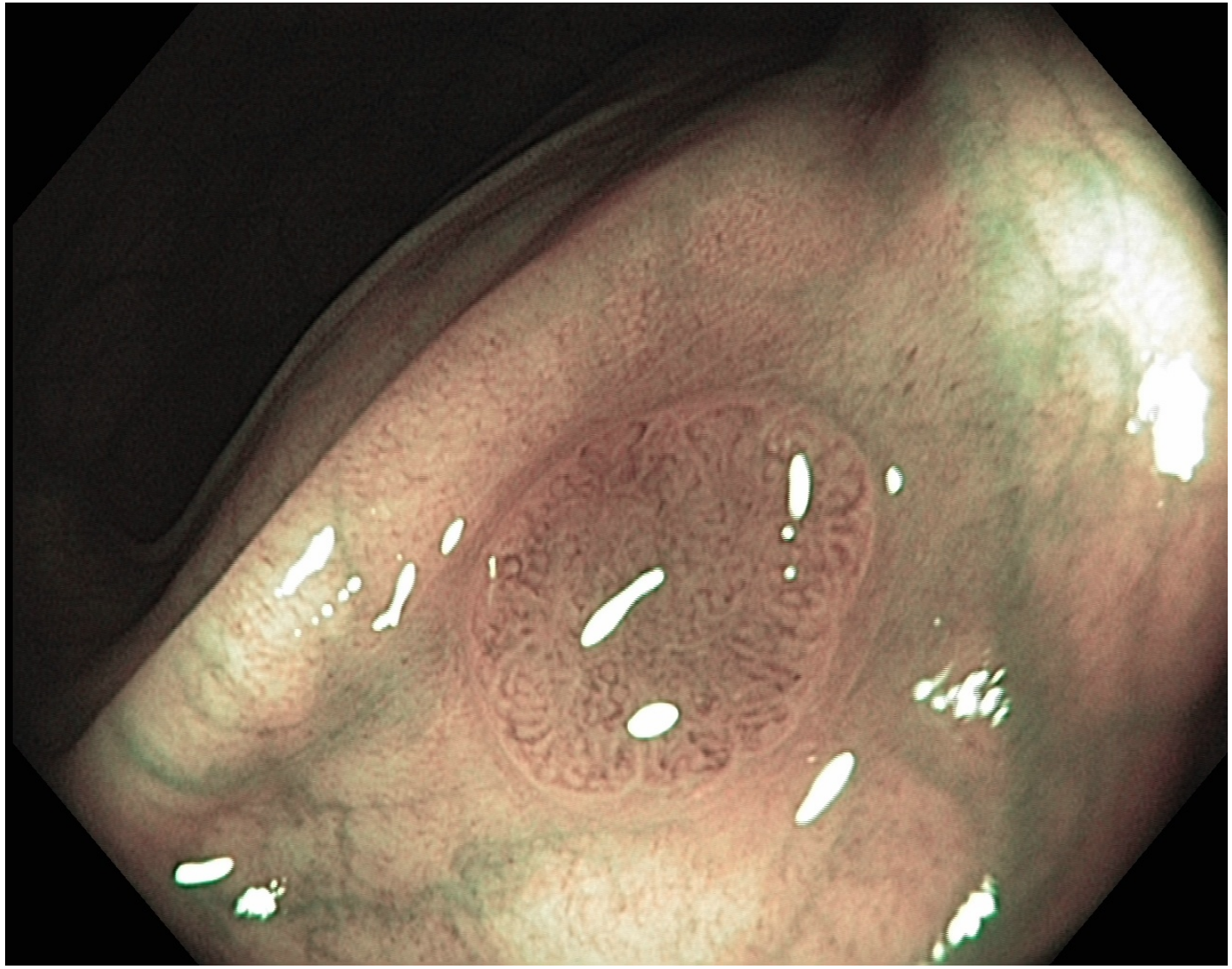
Features of Major Categories of Serrated Lesions

WHO classification	Prevalence	Shape	Size	Distribution	Malignant potential
Hyperplastic polyp	Very common	Sessile/flat	small	Mostly distal	Very low
Sessile serrated adenoma/ Polyp	Common	Sessile/flat	Big	80% proximal	Significant
Traditional serrated adenoma	Rare	Sessile/ pedunculated	Big	Mostly distal	Significant

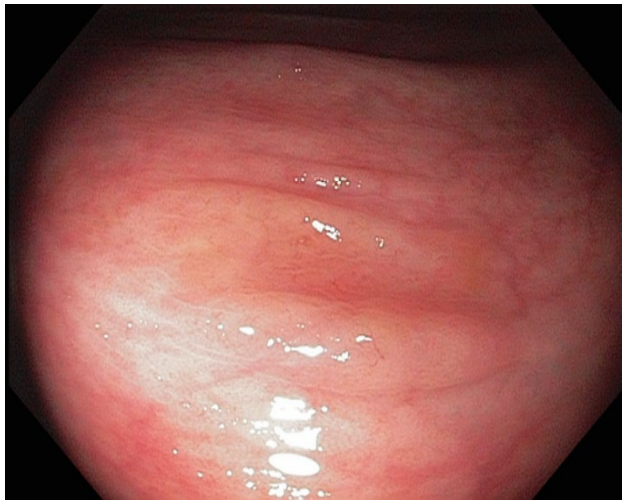
Spectrum of Pre-cancerous Lesions in the Colorectum

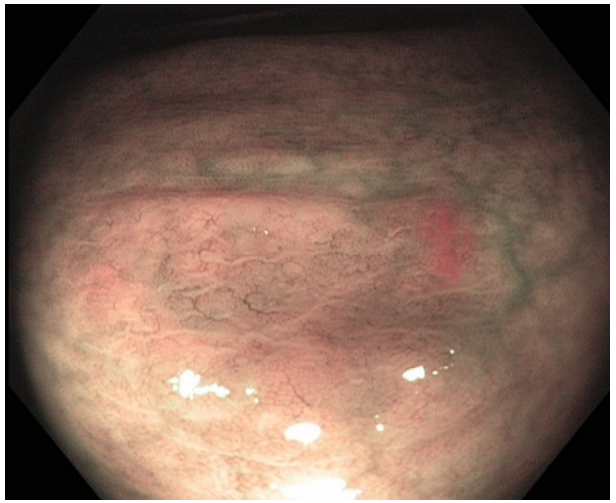
Lesion	Paris shape	Distribution	Prevalence	Pathology
Traditional adenomatous polyps	1p 1s	Left Throughout	Low Common	Mostly LGD Mostly LGD
Flat adenomas (lesions)	2a	Greater to right	Common	Mostly LGD
Depressed adenomas (lesions)	2c 2a + 2c 2c +2a	Greater to right	rare	↑↑ HGD and invasive cancer
Sessile serrated adenoma (polyp)	1s or 2a	Greater to right	Common	Distinction from HP may not be reliable
TSA	1s or 1p	Left colon	rare	Uncertain

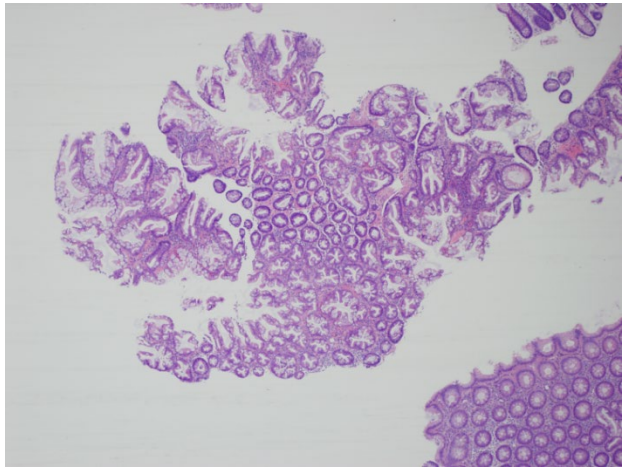


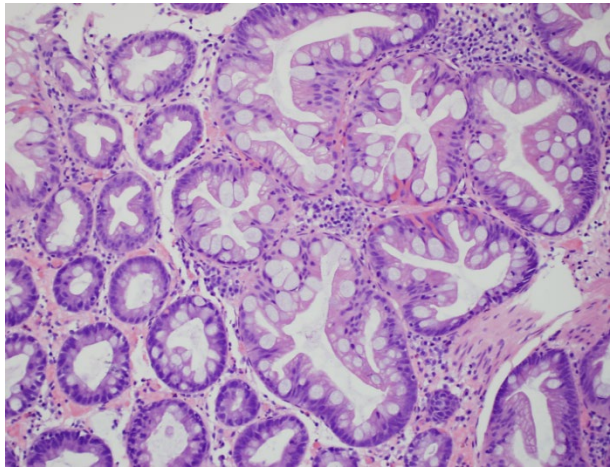


Pale, Sessile, Indistinct Edges, Lacy Blood Vessels

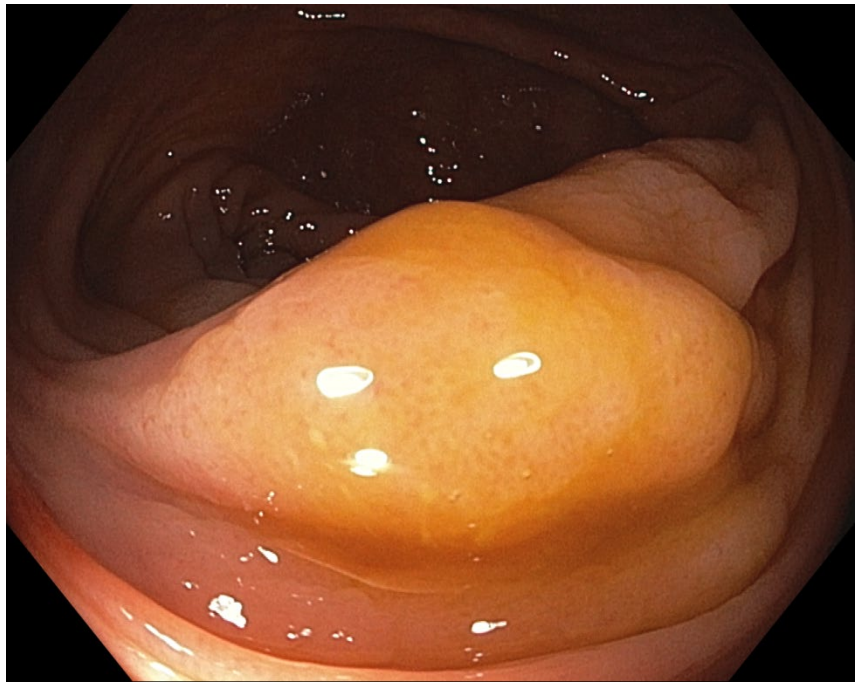


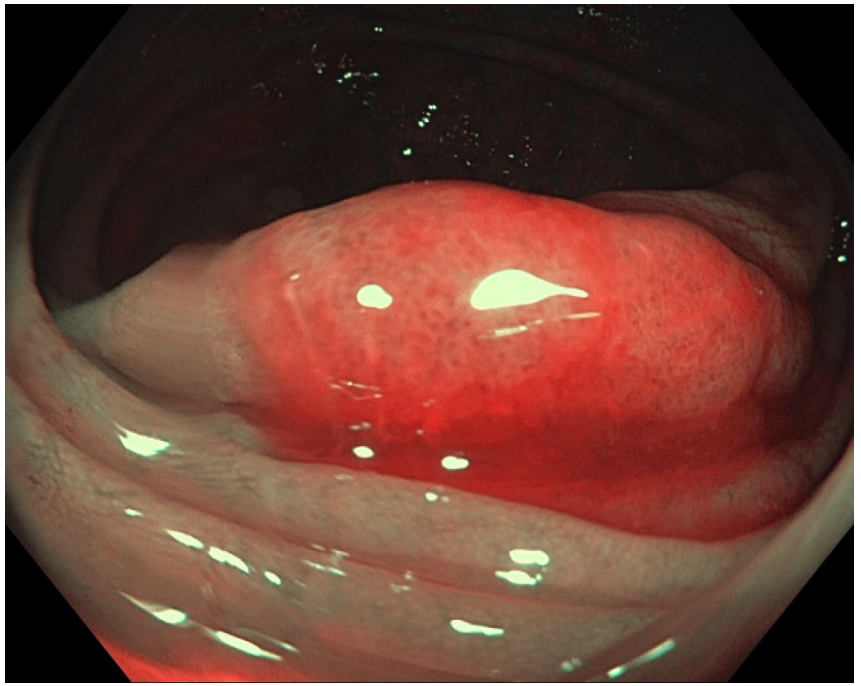


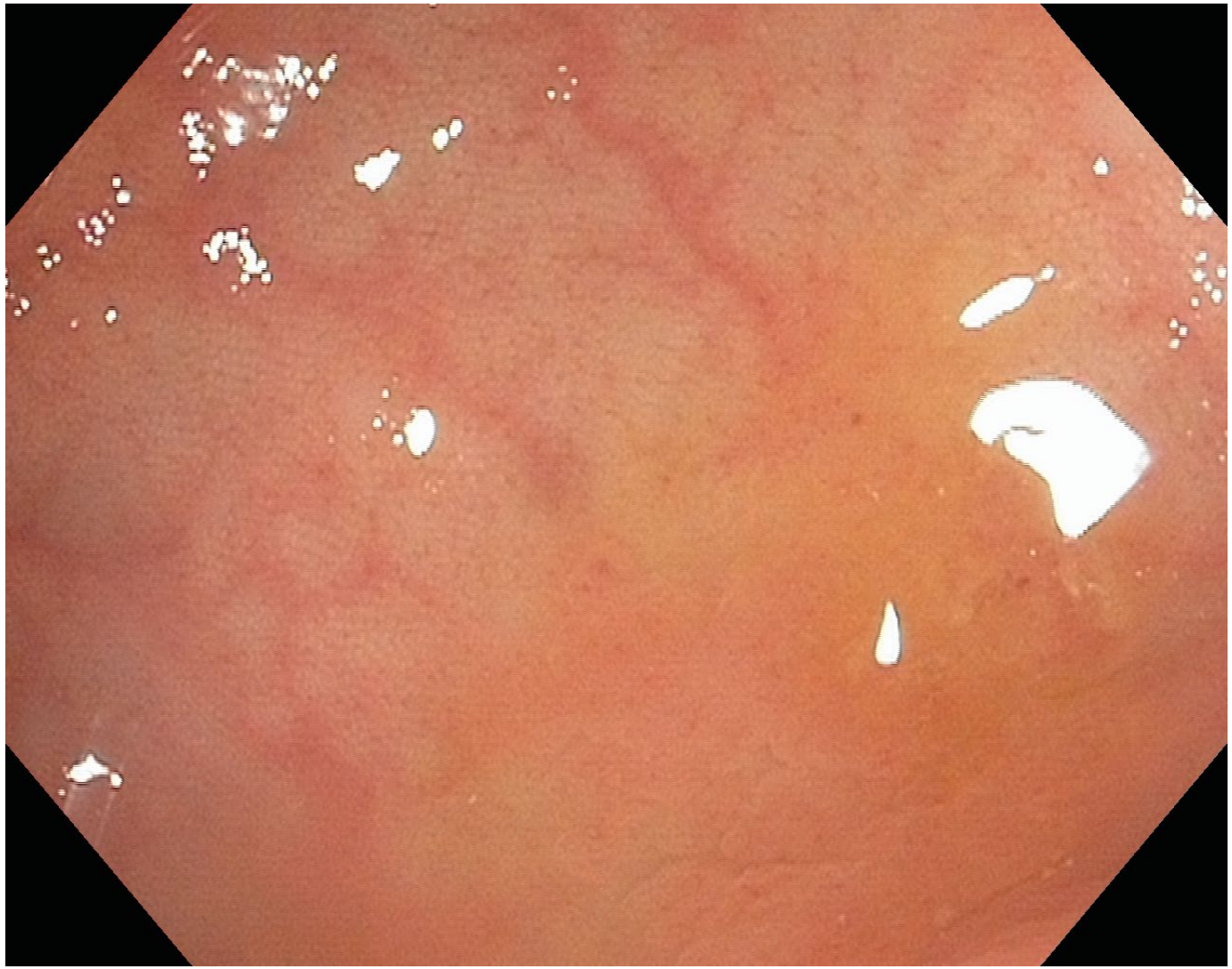




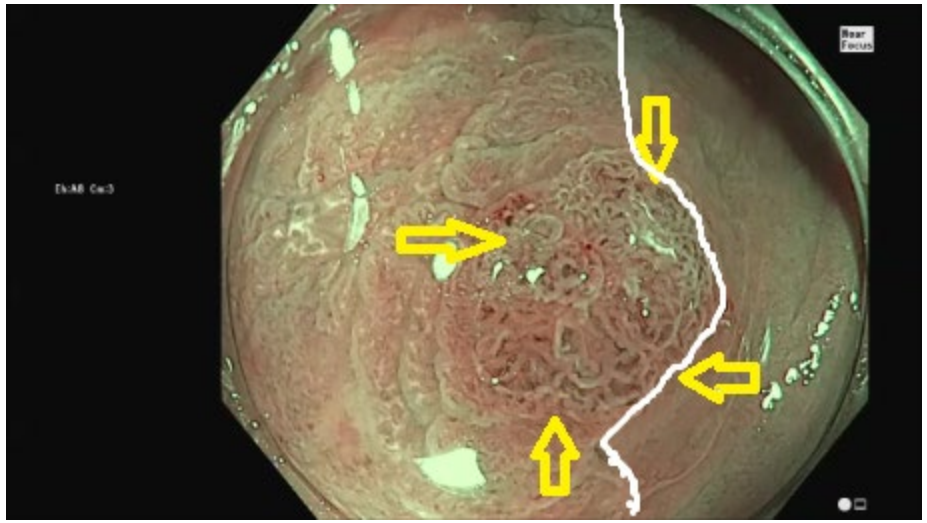
Serrated Lesion with Mucus Cap







SSP with Cytological Dysplasia



Changes in Epidemiology of Colorectal Cancer

- Major incidence declines since 1985
  - Accelerated declines in persons over age 50 beginning in 2000
- Incidence rates are rising in persons under age 50
  - % of all cases under age 50 has about doubled (7% → 15%)
  - USPSTF analysis suggested age 45 was most cost-effective age to begin screening
  - Aggressive evaluation of symptomatic patients recommended

USPSTF Screening Recommendations

- CRC screening has grade A recommendation
- No ranking of tests
- Offer screening from ages 45-75 years
  - Stop at 85
  - Individualize between age 75 and 85

American Cancer Society Recommendations

- Start screening at age 45
  - “qualified recommendation”
  - Based on modeling on new data on incidence rates
- No ranking of tests

Approaches to Screening

- Organized (programmatic)
  - Usually based on FIT
- Opportunistic (office-based)
  - Usually based on colonoscopy

Ways to Offer Screening

- Multiple options
  - Offering more than 2 options does not increase total adherence
- Sequential screening
  - May maximize adherence rates and maximize use of the most effective test
- Risk stratified screening
  - Offer FIT to younger persons especially women; colonoscopy to older persons

Multi-Society Task Force (ASGE, ACG and AGA)

- Begin screening at age 45
- Tests are ranked to make process of offering screening more practical:
  - Effectiveness
  - Cost-effectiveness
  - Evidence of uptake
  - Practical features

What Tests to Offer: MSTF Recommendations

- Tier 1
  - Colonoscopy every 10 years
  - Annual FIT
- Tier 2
  - Flex sig every 5-10 years
  - CTC every 5 years
  - Cologuard every 3 years
- Tier 3
  - Capsule colonoscopy
- Don’t use
  - Septin 9 plasma assay

Colonoscopy

- Provides longest interval of protection
- Gold standard and unmatched for cancer detection and polyp detection
- The only strategy that provides cancer ***prevention*** through polyp removal

Fecal Immunochemical Test (FIT)

- Stool test that checks for hemoglobin
- Assumes cancers will bleed
- Once a year
- Requires stool sample be obtained

FIT Testing

- Threshold for detection of hemoglobin
  - 20 µg/gram feces
- Advantages
  - Done at home
  - Low cost - $22
  - Better adherence in organized settings (Kaiser)
- If threshold for hemoglobin 10 µg/gram feces
  - Sensitivity for cancer: 91%

FIT Testing – Take Home Points

- Low cost
- Easy to use
- Good (but not great) sensitivity for CRC
  - Much improved if decreased for hemoglobin threshold
- Colonoscopy is needed if test is positive
- Only prevents cancer when it results in colonoscopy

FIT-Fecal DNA Test

- Currently available: Cologuard®
- Contains a FIT
- DNA assays:
  - K-ras
  - B-actin
  - NDRG4 and BMP3 methylation

Fecal DNA – The "Deep C" Trial - Imperiale et al NEJM 2014

Finding	N	Parameter	Fecal DNA	FIT
All CRC	64	Sensitivity	92.2%	73.4%
CRC I-III	60	Sensitivity	93.3%	73.3%
All Adv. Ad.	752	Sensitivity	42.4%	23.8%
AA ≥ 2 cm	116	Sensitivity	65.5%	43.1%
SSP ≥ 1 cm		Sensitivity	42.4%	5.1%
All else	9118	Specificity	86.6%	94.9%
No adenoma	6237	Specificity	89.8%	96.4%

TABLE 5. Advantages and limitations of the FIT-fecal DNA stool test for colorectal cancer screening

Advantages
Noninvasive
High (92%) sensitivity for cancer
Recommended at 3-year intervals (compared to 1 year for FIT)
Limitations
Less sensitive for cancer than high-quality colonoscopy
Less sensitive for adenomas and serrated lesions than colonoscopy
High (12%) false-positive rate
False-positive rate increases with patient age
Expensive ($500) compared to FIT ($22)
Most of the sensitivity derives from the FIT, which itself is inexpensive
Dominated by FIT in cost models: FIT is more effective and cost-effective than the FIT-fecal DNA test
No evidence to support use outside of screening
Basis for positive results (FIT or DNA stool tests, or both) is not reported
Colonoscopy for a positive FIT-fecal DNA test is considered part of the continuum of care for colon cancer screening. There is no out-of-pocket cost for the colonoscopy

Abbreviation: FIT, fecal immunochemical test.

Rex, D. PRACTICAL ADVICE FOR COLORECTAL CANCER SCREENING. GI & Hepatology News 2019

What Tests to Offer MSTF Recommendations

- Tier 1
  - Colonoscopy every 10 years
  - Annual FIT
- Tier 2
  - Flex sig every 5-10 years
  - CTC every 5 years
  - FIT-Fecal DNA Test (Cologuard®) every 3 years
- Tier 3
  - Capsule colonoscopy
- Don’t use
  - Septin 9 plasma assay

Colonoscopy Prevent CRC and CRC Mortality

Author Year	Country	Design	Primary endpoint	Residual risk
Kahi 2009	U.S.	Cohort	Incidence	0.33
Baxter 2009	Canada	Case-control	Mortality	0.63
Mulder 2010	Netherlands	Case-control	Incidence	0.56
Singh 2010	Canada	Cohort	Mortality	0.71
Brenner 2011	Germany	Case-control	Incidence	0.23
Baxter 2012	U.S.	Case-control	Mortality	0.40

Colonoscopy Prevents Right Sided Colon Cancer and Cancer Mortality

Author Year	Country	Design	Primary outcome	Risk
Brenner 2011	Germany	Case-control	Incidence	0.58
Baxter 2012	U.S.	Case-control	Mortality	0.44

Colonoscopy Protection May Be > 20 Years

Interval	Odds ratio	95% CI
1-2 years	0.14	0.10-0.20
3-4 years	0.12	0.08-0.19
5-9 years	0.26	0.18-0.39
10-19 years	0.28	0.17-0.45
≥ 20 years	0.40	0.24-0.66

Colonoscopy
– is Operator Dependent

Variable Detection of Adenomas Among GI Docs During Colonoscopy

	Number of doctors	Lowest ADR	Highest ADR	Range
Barclay Illinois 2006	12	9.4%	32.7%	3.5
Chen Indiana 2007	9	15.5%	41.1%	2.7
Imperiale Indiana 2009	25	7%	44%	6.3
Shaukat Minnesota 2009	51	10%	39%	3.9

Variable Detection of Proximal Serrated Lesions (GI Docs) During Colonoscopy

	Number of doctors	Lowest proximal colon serrated lesion detection rate	Highest proximal colon serrated lesion detection rate	Range
Hetzel Boston	13	1.1%	7.6%	6.9
Kahi Indiana	15	1%	18%	18

Operator Dependence – Cancer Prevention

Kaminski et al NEJM2010;362:1795-803

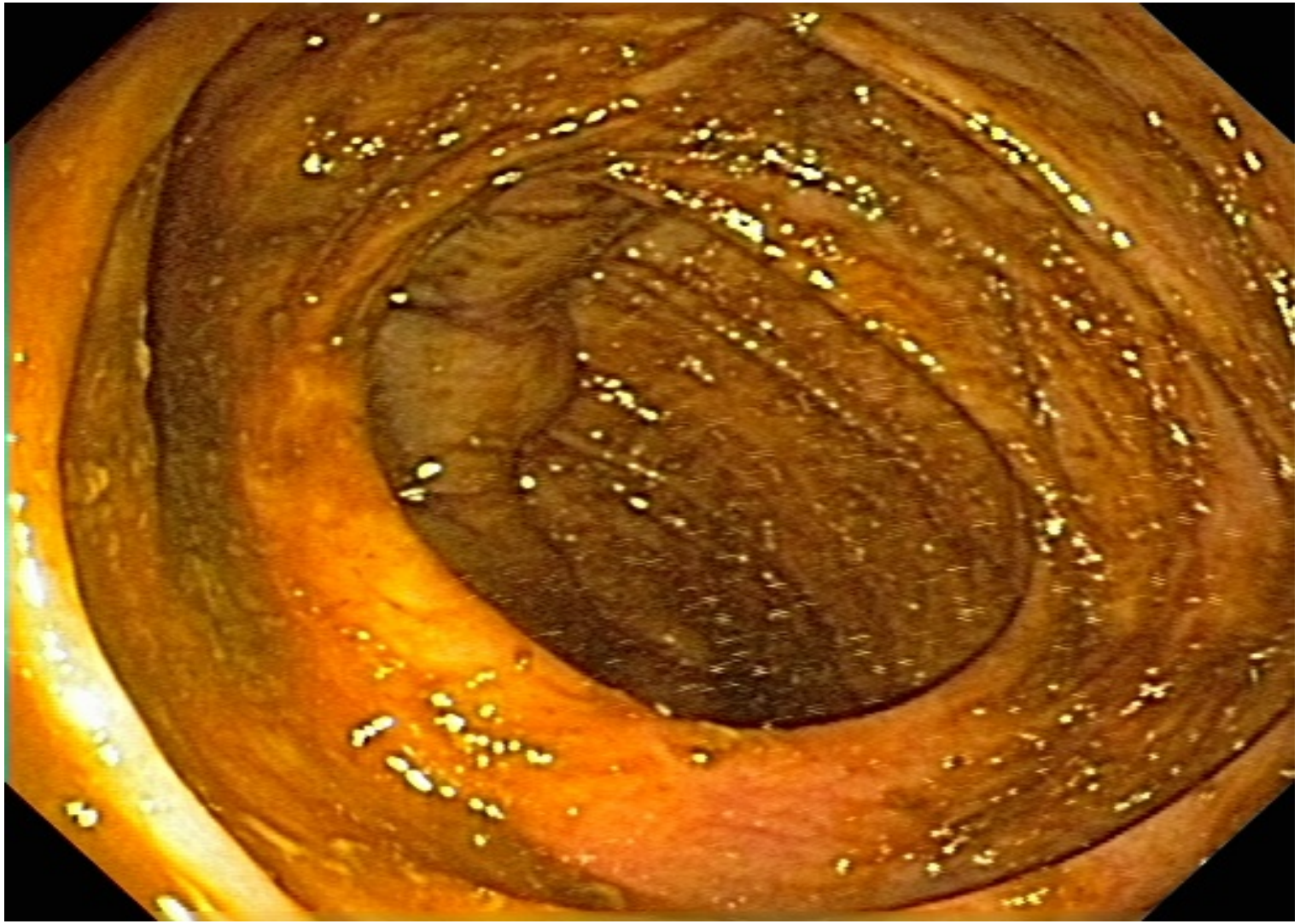
Adenoma detection rate (ADR)	Hazard ratio
< 11%	10.94
11.0 14.9%	10.75
15.0-19.9%	12.50

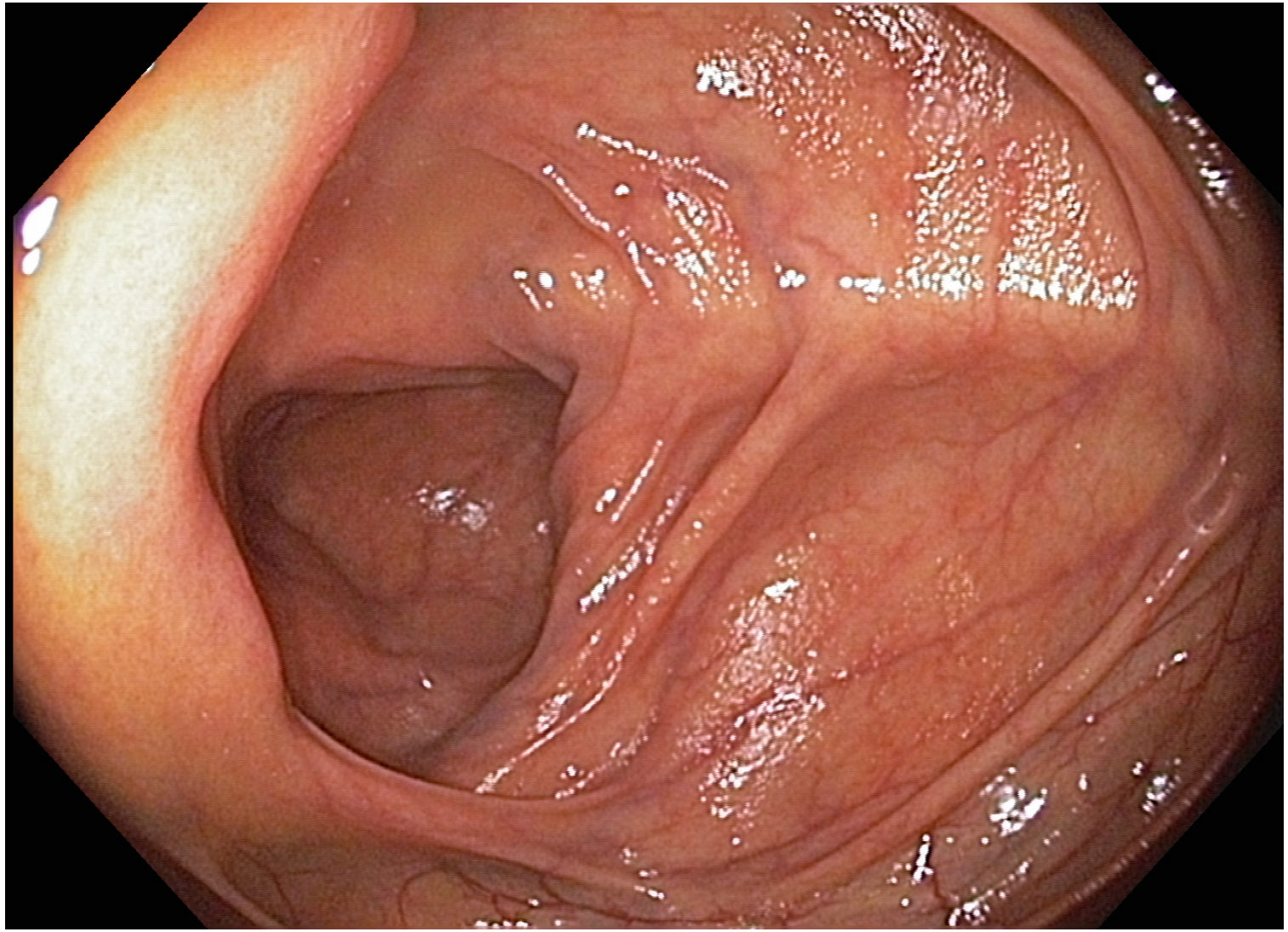
California Kaiser Study Validates the ADR

- > 700 interval cancers
- 3% reduction in the risk of interval cancer and a 5% reduction in mortality for each 1% increase in the ADR
    - Corley et al NEJM 2014; 370:1298-306

How Do I Get a Good Colonoscopy?

- Split-dose the preparation
- Ask your doctor for their ADR
    - Rex et al GIE;2017;86:18-33





Modifications to Screening Recs

- Start earlier if African-American (age 45)
- Family history
  - Always consider Lynch
  - Count FDRs
  - Consider age (60 year cut-off)
  - If ≥ 2 FDRs or 1 FDR < 60 then start at 40 or 10 years before the age at diagnosis of the youngest affected relative
    - Use colonoscopy at 5 year intervals

Post-Polypectomy Surveillance

Risk Stratification - Adenomas

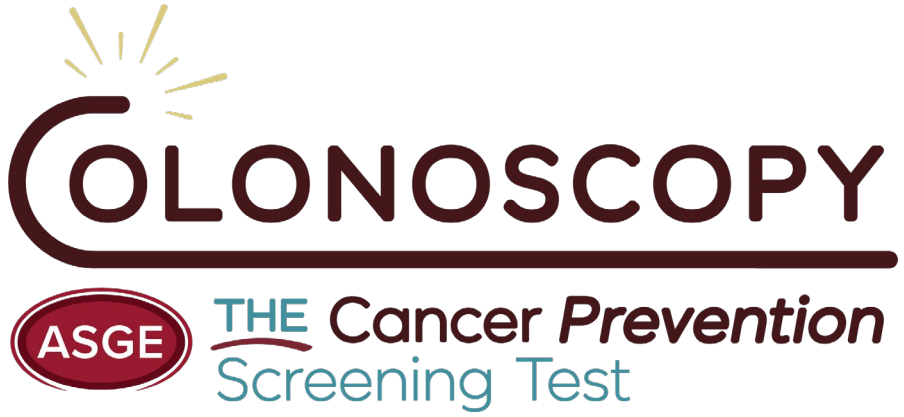
- Low risk adenomas
  - 1 or 2 tubular adenomas < 10 mm in size: 7-10 years
  - 3 or 4 tubular adenomas < 10 mm in size: 3-5 years
- High risk adenomas
  - Any adenoma ≥ 10 mm: 3 years
  - Any adenoma with villous elements or HGD: 3 years
  - 5-10 adenomas: 3 years
  - > 10 adenomas: 1 year

Risk Stratification - Serrated Lesions

- ≤ 20 HPs in rectum or sigmoid colon < 10 mm: 10 years
- ≤20 HPs proximal to sigmoid colon: 10 mm: 10 years
- 1-2 SSPs < 10 mm: 5-10 years
- 3-4 SSPs < 10 mm: 3-5 years
- 5-10 SSPs < 10 mm: 3 years
- SSP ≥ 10 mm: 3 years
- SSP with dysplasia: 3 years
- HP ≥ 10 mm: 3-5 years
- TSA: 3 years

Summary

- Pre-cancerous lesions: two main types that differ in appearance, amount of bleeding, colon location
- PCPs should encourage screening
- Screening: Colonoscopy q 10 or annual FIT
- Understand FIT-Fecal DNA
- Colonoscopists need to measure quality


COLONOSCOPY
ASGE
THE Cancer Prevention
Screening Test